Remarks

Applicant has provided a complete claim set for the convenience of the Examiner. No amendments have been made.

Rejections Under 35 U.S.C. § 112, First Paragraph

The Examiner rejected claims 10-18, 40-48 and 57-62 under 35 U.S.C. § 112, first paragraph, as not enabled. Applicant respectfully traverses the rejection.

As is well settled in patent law, the analysis of enablement should be commensurate with the scope of the claims. This was reinforced by the court in In re Wands 858 F.2d 731, 8 USPQ2d 1400, (Fed. Cir. 1988), in which the breadth of the claims is one of the enumerated factors recommended for consideration in a proper analysis of enablement. The Examiner bears the "initial burden of setting forth a reasonable explanation as to why [he/she] believes that the scope of protection provided by [the] claim is not adequately enabled by the description of the invention provided in the specification" when rejecting a claim as not enabled. *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993).

The Examiner has recognized that the claims are enabled for specific suppression of isolated killer T cells, but states that the claims are not enabled for specific suppression of killer T cells in a mixed population of cells or *in vivo*.

In support of the enablement rejection, the Examiner cites the Watt reference (Blood 84:200-210, 1994) for its description of wide expression of CEACAM1 (i.e., biliary glycoprotein). The Examiner notes that Applicant has demonstrated the suppression of propagated killer T cell lines and isolated killer T cells, but not killer T cells in a mixed population or *in vivo*. Based on this lack of a demonstration and the teachings of the Watt reference, the Examiner concludes that the claimed invention is not enabled because one of

ordinary skill in the art would not be able to reasonably predict that killer T cells could be suppressed in a mixed population, would not know how to target specifically killer T cells without also increasing cross-linking of CEACAM1 on other cells in a population or *in vivo*, and would not be able to predict the efficacy of the agent disclosed in the specification. In view of these alleged shortcomings of the specification, the Examiner suggests that one of ordinary skill in the art would be required to undertake "undue trials and errors" to practice the invention as claimed.

Applicant respectfully requests that the Examiner take into consideration the following facts when reconsidering the enablement rejection. Applicant has taught that intestinal epithelial cells have unique properties that allow specific suppression by increasing the cross-linking of biliary glycoprotein polypeptides. In the Specification, Applicant stated that :

> The studies contained herein describe the unexpected finding that, whereas biliary glycoprotein is constitutively expressed by IECs, it is an activation molecule on T cells adjacent to the epithelium. The study of peripheral blood T cells, on the other hand, show the unexpected result that biliary glycoprotein is constitutively expressed at low levels and upregulated by T-cell activation. This difference between iIELs and PBTs suggests that biliary glycoprotein expression may be actively suppressed in the epithelium under normal conditions....Using cytotoxicity, which is a major function of iIELs, as a measure, it appears that biliary glycoprotein on activated iIELs functions as an inhibitory molecule for CD3-directed cytotoxic activity. In this manner, biliary glycoprotein should be considered as a killer inhibitory receptor. (Specification, page 8, emphasis added)

Thus, Applicant has taught one of ordinary skill in the art that epithelial cells have unique properties and that these properties provide a means for specific suppression. Keeping in mind the high level of skill of the person of ordinary skill in the art, this guidance, *by itself*, is sufficient to permit one of ordinary skill in the art to reasonably predict that killer T cells could be suppressed in a mixed population, and that killer T cells could be targeted specifically without also increasing cross-linking of CEACAM1 on other cells in a population or *in vivo*.

Regarding *in vivo* applications, Applicant stated the following:

> Modulation of killer T cell activity by molecules which bind biliary glycoprotein expressed on the surface of killer T cells is useful for specifically enhancing or suppressing an immune response in vivo, which may be useful for the treatment of conditions related to immune function including autoimmune disease, cancer, and transplantation (e.g., bone marrow or organs). (Specification, page 9).

Applicant also provided guidance for one of ordinary skill in the art regarding molecules useful in the full scope of methods of the invention, i.e., molecules which bind biliary glycoprotein and modulate killer T cell activity. Biliary glycoprotein binding agents were stated to include: "antibodies and fragments thereof, ligands for biliary glycoprotein, fragments thereof and fusion proteins containing ligands or other biliary glycoprotein binding molecules" among other molecules. (Specification, page 9). This disclosure certainly provides one of ordinary skill in the art with sufficient guidance to practice the claimed invention throughout its scope.

In addition, further detailed guidance was provided regarding particular binding molecules. Certain molecules were described with even greater specificity, such as monoclonal antibodies:

> According to one embodiment, the biliary glycoprotein binding agent used in the invention is an intact anti-biliary glycoprotein monoclonal antibody in an isolated form, preferably in a soluble form, or in a pharmaceutical preparation. (Specification, page 10).

Additional description of monoclonal antibodies useful in the methods of the invention was provided by Applicant, particularly on pages 10-12 and 14 of the specification. Specific examples that were disclosed include the monoclonal antibodies 34B1, 5F4 and 26H7, which were described in the working examples. Screening methods useful for identifying biliary glycoprotein binding agents also were described in the specification, such as on pages 14-15.

The Examiner indicated a belief that the specification does not teach how to extrapolate the *in vitro* experimental results to use *in vivo*. Applicant respectfully disagrees. The use of the methods of the invention *in situ*, including *in vivo* and *ex vivo*, was described starting on page 15

of the specification. Guidance regarding administration and formulation of biliary glycoprotein binding agents is provided on pages 16-18.

Regarding the Examiner's statement that one of ordinary skill in the art would not be able to predict the efficacy of the agent disclosed in the specification, Applicant notes that a prediction of efficacy is not required for enablement. Instead, Applicant's specification must teach one of ordinary skill in the art to make and/or use the invention without the exercise of undue experimentation. The specification accomplishes this requirement.

As evidence of the adequacy of the specification's teachings, Applicant encloses herewith some additional data in the form of a declaration of the Applicant pursuant to 37 C.F.R 1.132. Applicant has performed and/or directed the performance of experiments consistent with the teachings contained in the specification regarding the use of the claimed invention for the suppression of killer T cells in a mixed population of cells, and in particular for the treatment of colitis *in vivo* as demonstrated in two separate hapten-mediated mouse models of colitis. See, Declaration of Richard S. Blumberg. The experiments required only routine experimentation in view of the teachings of the specification.

The results of the experiments reported in the Declaration of Richard S. Blumberg demonstrate that administering anti-CEACAM antibodies and a CEACAM1^{a}-Fc chimeric protein (for homophilic or heterophilic ligation of the CEACAM1^{a} N-domain on activated T cells, respectively), can be used to suppress specifically the cytotoxicity or proliferation of killer T cells *in vivo* in a subject, as is claimed. The *in vivo* experimental results provided in the Declaration of Richard S. Blumberg also clearly demonstrate specific suppression of killer T cells in a mixed population of cells.

The Declaration of Richard S. Blumberg therefore shows that the teachings of the specification are sufficient to permit one of ordinary skill in the art to practice the claimed invention without resort to undue experimentation. The results also demonstrate that the wide expression of CEACAM described in the Watt reference does not interfere with the practice of

the claimed methods. Therefore, Applicant asserts that the specification fully enables the claimed invention.

In view of the foregoing, Applicant respectfully requests that the Examiner reconsider and withdraw the rejection of claims 10-18, 40-48 and 57-62 under 35 U.S.C. § 112, first paragraph, as not enabled.

CONCLUSION

In view of the foregoing amendments and remarks, this application should now be in condition for allowance. In particular, claims 42-44 were rejected solely due to the lack of antecedent basis, and this deficiency has been remedied by amendment of the claims in accordance with the Examiner's suggestions. Accordingly, a notice of allowance is respectfully requested. If the Examiner believes, after this amendment, that the application is not in condition for allowance, the Examiner is requested to call the Applicant's attorney at the telephone number listed below.

If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time. If there is a fee occasioned by this response, including an extension fee, that is not covered by an enclosed check, please charge any deficiency to Deposit Account No. 23/2825.

Respectfully submitted,
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